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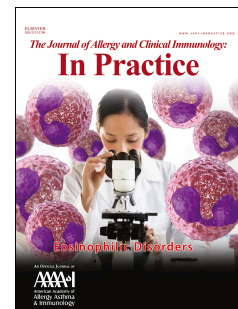
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Onset of Eosinophilic Esophagitis During a Clinical Trial Program of Oral Immunotherapy for Peanut Allergy

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Josh Brostoff, Trinh Pham, Robert Ryan are employees of Aimmune Therapeutics, a Nestlé Health Science company.

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Seema Aceves is a consultant for Regeneron and Gossamer; is an inventor of oral viscous budesonide, patented by the University of California, San Diego, and licensed by Shire/Takeda; and has received research funding from the Ferring Research Institute. For this study, Dr. Aceves reviewed the data submitted to the FDA and no longer has a relationship with Aimmune Therapeutics, a Nestlé Health Science company.

Daniel C. Adelman was an employee of Aimmune Therapeutics, a Nestlé Health Science company, at the time of submission and has patents pending for the following: US 16/542,198, PCT/US2019/046706, US 16/721,805, and PCT/US2019/067634.

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CLINICAL IMPLICATIONS

Eosinophilic esophagitis (EoE) occurring during Peanut (*Arachis hypogaea*) Allergen Powder-dnfp (PTAH) oral immunotherapy (OIT) was responsive to standard-of-care treatments and improved or resolved after PTAH discontinuation. The risk of developing EoE during OIT with PTAH in clinical trials was ~1% overall without inclusion of a portion of the 5% of participants who discontinued PTAH treatment because of gastrointestinal adverse events that were not further evaluated.

Keywords: AR101; eosinophilic esophagitis; food allergy; oral immunotherapy; PTAH; Peanut (*Arachis hypogaea*) Allergen Powder-dnfp oral immunotherapy

Eosinophilic esophagitis (EoE) is a chronic immune-inflammatory disease triggered by food and/or environmental allergens. EoE onset has been reported in patients given oral immunotherapy (OIT) for milk, egg, and peanut allergy.¹ Peanut (*Arachis hypogaea*) Allergen Powder-dnfp (PTAH; previously AR101) is an approved OIT for peanut allergy. PTAH is contraindicated in patients with a history of EoE and per the product label should be discontinued if EoE develops while on treatment.

Data for all participants in the PTAH clinical trial program were reviewed to identify participants with EoE as of December 15, 2018. Overall EoE incidence was calculated and outcomes were summarized along with baseline clinical characteristics, symptom presentation, and treatments received.

The PTAH clinical trial program includes 2 phase 2 trials and 6 phase 3 trials in which 1217 participants (aged 4 to 55 years) received PTAH.²⁻⁵ Of the 1217 PTAH-treated participants, 62 patients withdrew from the studies owing to gastrointestinal (GI) symptoms, 28 were referred for gastroenterology evaluation, 17 of whom underwent esophagogastroduodenoscopy (EGD), and 12 of those were diagnosed with EoE, yielding an EoE incidence of approximately 1%. The overall exposure-adjusted EoE event rate was 0.9 per 100 patient-years.

The 12 EoE cases occurred in 1 woman aged 33 years and 11 participants aged 4 to 17 years, 9 of whom were male (**Table I**). Asthma (n=11) was the most common comorbid atopic disease, followed by allergic rhinitis (n=10), other food allergies (n=9), and atopic dermatitis (n=5). Common presenting symptoms included globus sensation, gastroesophageal reflux, regurgitation, vomiting, and postprandial abdominal pain (**Table II**). In 11 cases, symptom

improvement or resolution occurred within 12 days to 12 months of PTAH discontinuation and standard-of-care EoE therapy initiation. The final case resolved after 12 months. Ten cases were considered related to PTAH treatment (4 had history of chronic or recurrent GI symptoms) and 2 were considered unrelated (GI symptoms may have been present before starting PTAH).

Three cases were classified as mild, 7 moderate, and 2 severe; none were considered serious.

The median (range) PTAH dose at EoE diagnosis was 160 mg (12–950 mg).

All 12 patients received medications for their symptoms; most (83.3%; n=10) were treated with a proton pump inhibitor (PPI) with or without a topical corticosteroid (fluticasone and/or budesonide, n=4). All but 1 participant discontinued treatment with PTAH after EoE diagnosis.

In 7 participants with available follow-up biopsy results provided by investigators, 5 had endoscopic findings consistent with resolved EoE (4/5 received PPI), and 2 had improved but not fully resolved EoE (both received PPI). Of the 2 with improved EoE, symptoms were not resolved in 1 participant >1 year after stopping PTAH, and follow-up biopsy data were unavailable for 1 participant; both were thought to be symptoms suggestive of EoE before study entry.

In this analysis of the PTAH clinical trial program, the overall incidence of EoE was approximately 1%, which is lower than previously reported rates of EoE with OIT for food allergies (2.7% in a meta-analysis and 5.1% in a recent retrospective review).^{1, 6} The etiology of EoE pathogenesis in the cases reported in the PTAH clinical trial program are not definitively known, but may include EoE present and not diagnosed before OIT, EoE preexisting but subclinical and exacerbated by OIT, or EoE triggered de novo by OIT. A recent cohort study

showed that 1 in 20 participants with immunoglobulin E (IgE)–mediated food allergy had EoE at baseline irrespective of exposure to OIT.⁷ Individuals with IgE-mediated food allergy, including peanut allergy, are at increased risk of developing EoE, and the risk increases with additional IgE-mediated food allergies. Our population had increased baseline risk, with 9 of the 12 patients (75%) also having additional food allergies.

It is unknown whether there was a subset of cases that would have had transient esophageal eosinophilia or developed EoE but did not undergo EGD. In a recent longitudinal placebo-controlled study examining serial endoscopic biopsies during peanut OIT, all the peanut-allergic participants had signs of epithelial barrier dysfunction at baseline and in some cases esophageal eosinophilia.⁸ The study demonstrated that most OIT-associated esophageal eosinophilia resolves during maintenance OIT and is not associated with clinical symptoms. Because the majority of participants in the PTAH clinical trials stopped the study drug around the time of EoE diagnosis, it is not known whether the eosinophilic infiltrate would have resolved with continued dosing.

The majority of EoE cases resolved and, in all cases, improved with discontinuation of PTAH and standard-of-care treatment. It has previously been noted that EoE reported during OIT can respond to removal of the allergen and standard-of-care medications similarly to spontaneously occurring EoE.⁹

This analysis is limited in that it includes cases from multiple clinical trials and cannot provide the same quality of evidence as a true longitudinal incidence study of EoE, in which baseline and follow-up EGDs would be performed irrespective of whether symptoms emerged with

PTAH. In addition, the low rate of EoE in our analysis may have been influenced by exclusion criteria in the clinical trials program. Owing to the need for esophageal biopsy to diagnose EoE, the incidence of EoE may be underestimated, and analysis is limited by the absence of baseline EGD with biopsy. We are unable to confirm whether a portion of the 62 (5%) participants who discontinued PTAH treatment because of GI adverse events may have had undiagnosed EoE. The long-term effects of asymptomatic eosinophilia are not established, but progression to structural disease that will ultimately cause symptomatic disease is possible. In clinical practice, GI symptoms suggestive of possible EoE may resolve following discontinuation of PTAH; however, if patients have GI symptoms that persist, then evaluation by a gastroenterologist is recommended. Further, referral to a gastroenterologist is recommended for patients receiving OIT who develop persistent GI symptoms concerning for EoE with those found to have EoE co-managed by allergy and gastroenterology. The importance of ruling out EoE in those with persistent GI symptoms is also highlighted by these data: 5/17 (30%) of subjects who had symptoms suggestive of EoE leading to endoscopy did not have EoE.

In conclusion, the rate of developing EoE with PTAH in this clinical trial program was ~1%, not including the 5% of participants who discontinued PTAH treatment because of GI adverse events that were not further evaluated. EoE occurring during PTAH OIT was responsive to standard-of-care treatments and improved or resolved after per protocol–recommended PTAH discontinuation.

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Table I. Baseline Characteristics of Participants With Diagnosed Eosinophilic Esophagitis Across All PTAH Studies

Study	Case No.	Age, y / Sex / Race	Country	Comorbid Allergic Diseases	Baseline Peanut-Specific IgE, kU_A/L
ARC001 (NCT01987817)	1	4 / M / White	United States	Atopic dermatitis, asthma, allergic rhinitis	>100
ARC002 (ARC001 follow-on; NCT02198664)	2	8 / M / White	United States	Allergic rhinitis, other food allergies	5.3
ARC003 (PALISADE; NCT02635776)	3	10 / M / White	United States	Allergic rhinitis, asthma, atopic dermatitis, other food allergies	351.5
ARC004 (PALISADE follow-on; NCT02993107)	4	13 / F / Other*	United States	Allergic rhinitis, atopic dermatitis, asthma, other food allergies	268
	5	33 / F / White	United States	Allergic rhinitis, asthma	19.5
	6	9 / M / White	United States	Asthma, other food allergies	294.5

ARC007 (RAMSES; NCT03126227)	7	9 / M / White	United States	Asthma, other food allergies	277
	8	17 / M / White	Canada	Allergic rhinitis, asthma, other food allergies	17.1
ARC008 (NCT03292484)	9	14 / M / White	United States	Allergic rhinitis, atopic dermatitis, asthma, other food allergies	304.5
	10	17 / M / White	Canada	Allergic rhinitis, atopic dermatitis, asthma, other food allergies	70.3
	11	13 / F / White	United States	Allergic rhinitis, asthma, other food allergies	62.2
	12	15 / M / Other*	United States	Asthma, allergic rhinitis, allergic conjunctivitis	81.3

F, female; IgE, immunoglobulin E; M, male; PTAH, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp.

*Not reported.

Table II. Clinical Characteristics of Eosinophilic Esophagitis Cases Across All PTAH Studies

Case No.	Relevant Medical History	PTAH Dose at EoE Diagnosis, mg	Total Exposure to PTAH, d		Symptoms	Severity [†]	Initial Esophageal Biopsy Results	Repeat Esophageal Biopsy Results [‡]	Treatment	Relatedness to PTAH [†]
			At First GI Symptom Onset	At EoE Diagnosis						
1		12	58	58	Intermittent vomiting, abdominal pain, sore throat	Mild	EoE with peak eosinophil count of 92 eos/hpf	Biopsy performed – results NA [§]	Esomeprazole for vomiting; swallowed fluticasone after EoE diagnosis, elimination diet	Related
2	Gastroesophageal reflux during infancy and chronic regurgitation	950 [¶]	58	428	Frequent regurgitating/spitting up, gastric reflux	Moderate	The peak eosinophil count was 32 eos/hpf in the distal esophagus, 7 eos/hpf in the mid-esophagus, and up to 61 eos/hpf in the proximal esophagus	NR	Ranitidine, omeprazole, lansoprazole	Related
3	Gastroesophageal reflux; recurrent nausea and cough	200	30	176	Gastroesophageal reflux, recurrent nausea and cough, globus sensation	Mild	EoE; esophageal mucosa with intraepithelial eosinophilic infiltrates, degranulation, and plaques with bacteria; basal zone hyperplasia; fibrotic lamina propria	Improved with 22 eos/hpf	Omeprazole, elimination diet	Related
4	GI symptoms including abdominal pain	12	Occurred on placebo in parent study	49	Stomach pain	Severe	Eosinophil count of 195/ hpf distally and 140/hpf in the mid-esophagus	No evidence of eosinophil infiltration in the esophageal squamous mucosa	Lansoprazole	Not related
5	Dysphagia	200	2	544	Esophageal dysphagia	Severe	Proximal and distal biopsies showed fragments of squamous mucosa with basal cell hyperplasia, intercellular edema, marked reactive changes, and markedly increased numbers of intraepithelial eosinophils and lymphocytes	Mild active esophagitis with rare eosinophils	Budesonide, prednisone, fluticasone, ranitidine	Related
6		300	1	372	Abdominal pain	Moderate	Proximal esophagus squamous mucosa with mild chronic inflammation and eosinophilic infiltrate up to 50 eos/hpf; distal and mid-esophagus squamous mucosa without abnormality	NR	Calcium carbonate, omeprazole	Related

7		40	1	138	Emesis; globus sensation	Moderate	Squamous mucosa with increased intraepithelial eosinophils up to 68 eos/hpf in the proximal esophagus and up to 62 eos/hpf in the distal esophagus	First follow-up with submucosal fibrosis and squamous mucosa with increased intraepithelial eosinophils with up to 18 eos/hpf in the proximal esophagus and up to 25 eos/hpf in the distal; consistent with partially treated EoE Second follow-up 2–3 eos/hpf in proximal esophagus and 22 eos/hpf in the distal; no lymphocytes or submucal fibrosis	Omeprazole	Related
8	Postprandial abdominal pain, dysphagia	80	45	79	Postprandial abdominal pain; dysphagia	Mild	Intraepithelial eosinophils with a peak of ~25 eos/hpf and basal cell hyperplasia and ridge elongation in the proximal esophagus; focal mild basal cell hyperplasia in the distal esophagus	Follow-up EGD not performed	Lansoprazole, topical budesonide	Not related
9	Dysphagia	160	1	788	Dysphagia	Moderate	Proximal and mid esophagus with moderate esophagitis with abundant eosinophils; distal esophagus with mild esophagitis with abundant eosinophils (up to 215 eos/hpf)	Multiple repeat EGDs with eventual decreasing degree of eosinophilia	Esomeprazole, budesonide	Related
10		240	1	640	Abdominal pain, dysphagia, nausea, vomiting, gagging, reflux, decreased appetite	Moderate	Investigator report that biopsy consistent with EoE diagnosis, but pathology report not available	Multiple repeat EGDs with improvement with most recent biopsy showing up to 6 eos/hpf in the distal esophagus and up to 2 eos/hpf in the mid-esophagus	Pantoprazole, rabeprazole, fluticasone, budesonide	Related

11		160	1	225	Dysphagia, throat irritation and tightness, abdominal pain, heartburn	Moderate	Superficial esophageal squamous mucosa with histological changes compatible with EoE with up to 144 eos/hpf in the proximal esophagus and up to 113 eos/hpf in the distal	Second EGD with proximal and distal biopsies with superficial squamous mucosa with >100 eos/hpf; third EGD with normal biopsies per investigator report	Swallowed fluticasone	Related
12		40**	3	188	Emesis, GI upset unspecified	Moderate	Distal and mid-esophageal biopsies favored EoE with up to 12 eos/hpf distally and up to 15 eos/hpf in the mid-esophagus	Follow-up EGD not performed	Omeprazole	Related

EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos, eosinophils; GI, gastrointestinal; hpf, high-power field; NA, not available; NR, not reported; PTAH, Peanut (*Arachis hypogaea*) Allergen Powder-dnfp.

[†] As determined by the investigator.

[‡] Based on ongoing follow-up.

[§] EGD was performed at an outside facility; report not received by study site at time of follow-up.

[¶] The open-label ARC002 study allowed for up dosing up to a maximum of 2000 mg daily.

^{||} Dose was reduced to 200 mg 2 weeks before developing EoE.

****** Last dose before treatment discontinuation. EoE was diagnosed 52 days after treatment discontinuation.

Note: Treatments were not all necessarily given at the same time and may have been given in sequence.